APPLICANT(S): ARBIT Ehud et al.
SERIAL NO.: 10/500,822
FILED: March 14, 2005
Page 2

AMENDMENTS TO THE CLAIMS

Please amend claims 59, 79, 80, 82-88, 89, 92, 102, 103, 105, 108, 110, 117, 118, 120-122 and 128-131, as indicated below.

This listing of claims will replace all prior versions, and listings, of the claims in this application.

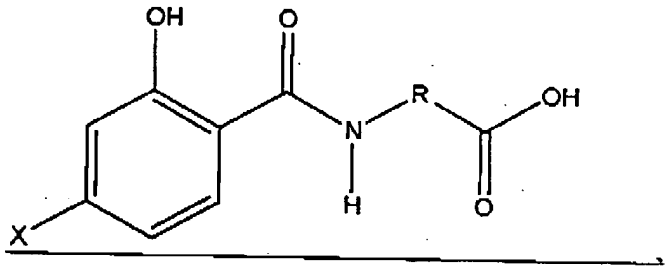
Listing of Claims

1-58. (Canceled)

59. (Currently Amended) An oral dosage form comprising

a dose of unmodified insulin, and

an effective amount of a delivery agent of the formula or a pharmaceutically acceptable salt thereof:



wherein

i. X is hydrogen or halogen; and

ii. R is substituted or unsubstituted C1-C3 alkylene, substituted or unsubstituted C1-C3 alkenylene, substituted or unsubstituted C1-C3 alkyl (arylene), substituted or unsubstituted C1-C3 aryl (alkylene),

wherein said dosage form ~~that~~ achieves a therapeutically effective reduction in blood glucose after oral administration to a human diabetic patient as compared to an untreated diabetic patient.

60. (Previously Presented) The oral dosage form of claim 59, wherein said dose of unmodified insulin achieves a comparable reduction in blood glucose concentration in human diabetic patients compared to a subcutaneous insulin injection in those patients, while providing a lower

plasma concentration of insulin in the peripheral circulation under acute, sub-acute or chronic conditions as compared to the peripheral plasma insulin concentration obtained via the subcutaneous injection.

61. (Previously Presented) The oral dosage form of claim 60, wherein said lower plasma insulin concentration is at least about 20%.

62. (Previously Presented) The oral dosage form of claim 59, wherein said oral dosage form provides a ratio of portal vein to peripheral plasma insulin concentration from about 2.5:1 to about 6:1.

63. (Previously Presented) The oral dosage form of claim 59, wherein said dosage form is solid.

64. (Previously Presented) The oral dosage form of claim 59, wherein the oral dosage form provides a t_{max} for plasma insulin concentration at a time point from about 0.1 to about 1.5 hours after oral administration to said patients.

65. (Previously Presented) The oral dosage form of claim 64, wherein at least about 80% of the blood glucose concentration reduction caused by said dose of insulin occurs within about 2 hours after oral administration of said dosage form.

66. (Previously Presented) The oral dosage form of claim 59, wherein said dosage form upon pre-prandial oral administration to human diabetic patients causes the mean blood glucose concentration in said patients to be reduced for the first hour after oral administration relative to a mean baseline (fasted) blood glucose concentration in said patients.

67. (Previously Presented) The oral dosage form of claim 59, wherein said oral dosage form upon pre-prandial oral administration provides a mean blood glucose concentration which does not vary by more than about 40% for the first hour after oral administration, relative to a mean baseline (fasted) blood glucose concentration in said patients, where a meal is eaten by said patients within about one half hour of oral administration of said dosage form.

68. (Previously Presented) The oral dosage form of claim 59, which provides a mean blood glucose concentration which does not vary by more than about 30% for the first hour after oral administration.

69. (Previously Presented) The oral dosage form of claim 59, wherein said dose of insulin achieves a t_{max} for plasma insulin concentration at a time point from about 0.25 to about 1.5 hours after oral administration to a human diabetic patient, and upon preprandial administration to the patient provides effective control of blood glucose concentration in response to a meal as manifested by providing a blood glucose concentration which does not vary by more than about 40% for the first hour after oral administration from the baseline (fasted) blood glucose concentration in the patient, and provides a return to baseline plasma insulin levels in the patient no later than 4 hours after oral administration.

70. (Previously Presented) The oral dosage form of claim 69, wherein the insulin is a form of human regular insulin.

71. (Previously Presented) The oral dosage form of claim 69, wherein the oral dosage form is solid.

72. (Previously Presented) The oral dosage form of claim 59, wherein the oral dosage form is in the form of a tablet or capsule.

73. (Previously Presented) The oral dosage form of claim 59, wherein the dose of unmodified insulin contained in the dosage form is from about 50 Units to about 600 Units (from about 2 to about 23mg).

74. (Previously Presented) The oral dosage form of claim 59, wherein the dose of unmodified insulin contained in the dosage form is from about 100 Units (3.8 mg) to about 400 Units (15.3 mg) insulin.

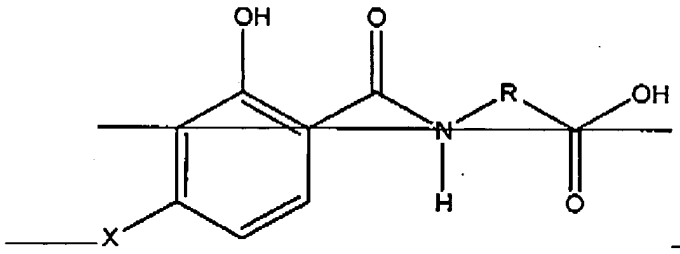
75. (Previously Presented) The oral dosage form of claim 59, wherein the dose of unmodified insulin is from about 150 Units (5.75 mg) to about 300 Units (11.5 mg).

76. (Previously Presented) The oral dosage form of claim 59, which provides a t_{max} for plasma insulin concentration at about 0.1 to about 1.5 hours after oral administration.

77. (Previously Presented) The oral dosage form of claim 59, which provides a t_{max} for plasma insulin concentration at about 0.25 to about 0.5 hours after oral administration.

78. (Previously Presented) The oral dosage form of claim 59, wherein the dosage form begins delivering insulin into the portal circulation to achieve peak levels within about 30 minutes or less.

79. (Currently Amended) The oral solid dosage form of claim 59, ~~further comprising an effective amount of a~~ wherein said delivery agent ~~of the formula or a pharmaceutically acceptable salt thereof,~~



~~wherein~~

~~i. X is hydrogen or halogen; and~~

~~ii. R is substituted or unsubstituted C1-C3 alkylene, substituted or unsubstituted C1-C3 alkenylene, substituted or unsubstituted C1-C3 alkyl (arylene), substituted or unsubstituted C1-C3 aryl (alkylene)~~ is 4-[(4-chloro, 2-hydroxybenzoyl)amino]butanoic acid .

80. (Currently Amended) The oral solid dosage form of ~~claim 79~~ claim 59, wherein X is a halogen.

81. (Previously Presented) The oral solid dosage form pharmaceutical composition of claim 80, wherein said halogen is chlorine.

82. (Currently Amended) The oral solid dosage form of ~~claim 79~~ claim 59, wherein R is C3 alkylene.

83. (Currently Amended) The oral solid dosage form of ~~claim 79~~ claim 59, wherein said peak plasma delivery agent concentration occurs within two hours of oral administration.

84. (Currently Amended) The oral solid dosage form of ~~claim 79~~ claim 59, wherein said delivery agent is 4-[(4-chloro, 2-hydroxybenzoyl)amino]butanoic acid.

85. (Currently Amended) The oral solid dosage form of ~~claim 79~~ claim 59, which provides a peak plasma delivery agent concentration that is from about 1,000 to about 100,000 ng/ml within about 0.1 to about 1.5 hours after oral administration.

86. (Currently Amended) The oral solid dosage form of ~~claim 79~~ claim 59, which produces a maximal decrease in blood glucose in treated patients from about 0.1 to 1 hour post oral administration.

87. (Currently Amended) The oral solid dosage form of ~~claim 79~~ claim 59, which produces a maximal decrease in blood glucose in treated patients at about 40 minutes post oral administration.

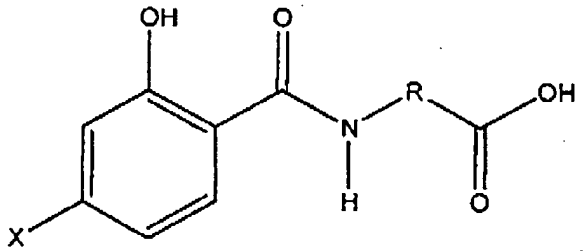
88. (Previously Presented) The oral solid dosage form of ~~claim 79~~ claim 59, which produces a decreased blood glucose in fasted human patients by at least 10% within one hour post oral administration.

89. (Currently Amended) The oral dosage form of claim 59, ~~further comprising an~~ wherein said effective amount of a pharmaceutically acceptable delivery agent ~~that~~ facilitates absorption of said insulin from the gastrointestinal tract of human diabetic patients, ~~and~~ said oral dosage form being capable of being orally administered to a human diabetic patient to provide a therapeutic effect.

90. (Previously Presented) The oral dosage form of claim 89, wherein the effective amount of said delivery agent is from about 1 mg to about 800 mg.

91. (Previously Presented) The oral dosage form of claim 89, wherein the effective amount of said delivery agent is from about 100 mg to about 600 mg.

92. (Currently Amended) A method of treating impaired glucose tolerance, achieving glucose homeostasis, treating early-stage diabetes, or treating late-stage diabetes, comprising administering to a human patient an oral dosage form ~~of~~ comprising unmodified insulin and an effective amount of a delivery agent of the formula or a pharmaceutically acceptable salt thereof,



, wherein

i. X is hydrogen or halogen, and

ii. R is substituted or unsubstituted C1-C3 alkylene, substituted or unsubstituted C1-C3 alkenylene, substituted or unsubstituted C1-C3 alkyl (arylene), substituted or unsubstituted C1-C3 aryl (alkylene),

which dosage form ~~that~~ achieves a therapeutically effective reduction in blood glucose after oral administration to a human diabetic patient.

93. (Previously Presented) The method of claim 92, wherein the oral dosage form is administered on a chronic basis.

94. (Previously Presented) The method of claim 92, wherein the unmodified insulin that achieves a comparable reduction in blood glucose concentration in human diabetic patients compared to a subcutaneous insulin injection in those patients, while providing a lower concentration of insulin in the peripheral blood circulation under acute, sub-acute or chronic conditions as compared to the peripheral plasma insulin concentration obtained via the subcutaneous injection.

95. (Previously Presented) The method of claim 92, wherein the unmodified insulin that achieves a therapeutically effective reduction in blood glucose after oral administration to a human diabetic patient and provides a ratio of portal vein to peripheral plasma insulin concentration from about 2.5:1 to about 6:1.

96. (Previously Presented) The method of claim 92, wherein the unmodified insulin that achieves a therapeutically effective reduction in blood glucose after oral administration to a human diabetic patient, wherein the dose of unmodified insulin is from about 100 Units (3.8 mg) to about 400 Units (15.3 mg) insulin.

97. (Previously Presented) The method of claim 92, wherein the unmodified insulin that achieves a therapeutically effective reduction in blood glucose after oral administration to a human diabetic patient and that provides a t_{max} for plasma insulin concentration at about 0.1 to about 1.5 hours after oral administration.

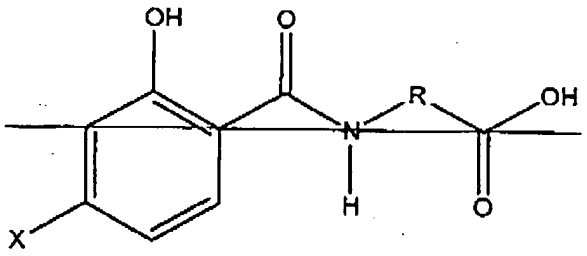
98. (Previously Presented) The method of claim 92, wherein the unmodified insulin that achieves a therapeutically effective reduction in blood glucose after oral administration to a human diabetic patient and that provides a t_{max} for plasma insulin concentration at about 0.25 to about 0.5 hours after oral administration.

99. (Previously Presented) The method of claim 92, wherein the unmodified insulin that achieves a therapeutically effective reduction in blood glucose after oral administration to a human diabetic patient, wherein the dosage form begins delivering insulin into the portal circulation (via absorption through the mucosa of the stomach) to achieve peak levels within about 30 minutes or less.

100. (Previously Presented) The method of claim 92, wherein said dosage form is solid.

101. (Previously Presented) The method of claim 100, wherein the solid dosage form is in the form of a tablet or capsule.

102. (Currently Amended) The method of claim 92, wherein said ~~dosage form further comprises an effective amount of a~~ delivery agent ~~of the formula or a pharmaceutically acceptable salt thereof,~~



~~wherein~~

~~i. X is hydrogen or halogen; and~~

~~ii. R is substituted or unsubstituted C1-C3 alkylene, substituted or unsubstituted C1-C3 alkenylene, substituted or unsubstituted C1-C3 alkyl (arylene), substituted or unsubstituted C1-C3 aryl (alkylene)~~ is 4-[(4-chloro, 2-hydroxybenzoyl)amino]butanoic acid.

103. (Currently Amended) The oral solid dosage form of ~~claim 102~~ claim 92, wherein X is a halogen.

104. (Previously Presented) The method of claim 103, wherein said halogen is chlorine.

105. (Currently Amended) The method of ~~claim 102~~ claim 92, wherein R is C3 alkylene.

106. (Currently Amended) A method of providing a therapeutically effective orally administrable unit dose of unmodified insulin, comprising combining from about 2 to about 23 mg of unmodified insulin with from about 1 to about 800 mg of a pharmaceutically acceptable delivery agent 4-[(4-chloro, 2-hydroxybenzoyl)amino]butanoic acid that facilitates absorption of said insulin from the gastrointestinal tract of human diabetic patients, and orally administering said unit dose to a human diabetic patient to provide a therapeutic effect.

107. (Previously Presented) The method of claim 106, wherein said pharmaceutically acceptable delivery agent is from about 100 mg to about 600 mg

108. (Currently Amended) A method of treating a human diabetic patient, comprising orally administering an oral dosage form comprising an effective dose of insulin and a pharmaceutically acceptable delivery agent 4-[(4-chloro, 2-hydroxybenzoyl)amino]butanoic acid pre-prandially to a human diabetic patient, such that an insulin t_{max} at a time point from about

0.25 to about 1.5 hours after oral administration is attained and blood glucose concentration of the patient is effectively controlled in response to the meal as manifested by providing a blood glucose concentration which does not vary by more than about 40% for the first hour after oral administration from the baseline (fasted) blood glucose concentration in the patient, and which provides a return to baseline plasma insulin levels in the patient no later than 4 hours after oral administration.

109. (Previously Presented) The method of claim 108, wherein the insulin included in said oral dosage form is a human regular insulin.

110. (Currently Amended) A method of treating diabetics, comprising orally administering to diabetic patients on a chronic basis an oral insulin treatment comprising a dose of unmodified insulin together with a delivery agent 4-[(4-chloro, 2-hydroxybenzoyl)amino]butanoic acid that facilitates the absorption of the insulin from the gastrointestinal tract to provide a therapeutically effective reduction in blood glucose and a peak blood plasma insulin concentration that is reduced relative to the peak blood plasma insulin concentration of an equivalent therapeutically effective reduction in blood glucose concentration achieved by subcutaneous injection of insulin.

111. (Previously Presented) The method of claim 110, wherein the incidence of a disease state associated with chronic insulin administration is reduced as a result of said chronic administration.

112. (Previously Presented) The method of claim 110, wherein the method provides a reduced expression of genes associated with vascular disease as compared to the level of expression of genes associated with vascular disease resulting from an equivalent reduction in blood glucose concentration achieved in a population of patients via subcutaneous injection of insulin.

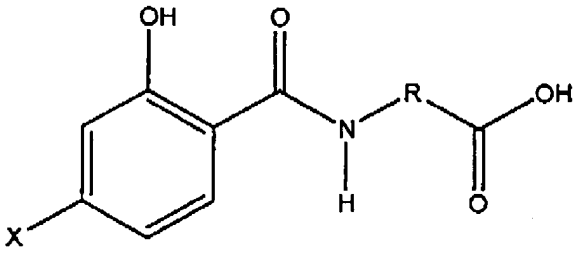
113. (Previously Presented) The method of claim 112, wherein the genes associated with vascular disease are selected from the group consisting of early response genes, genes associated with cytokines, genes associated with adhesion molecules, genes associated with lipid peroxidation, genes associated with thrombosis and combinations thereof.

114. (Previously Presented) The method of claim 113, wherein the early response genes are selected from the group consisting of c-myc, jun B, Egr-1, Ets-1 and combinations thereof.

115. (Previously Presented) The method of claim 110, wherein plasminogen activator inhibitor concentrations resulting from the method are lower as compared to the plasminogen activator inhibitor concentrations resulting from an equivalent therapeutically effective reduction in blood glucose concentration achieved by subcutaneous injection of insulin.

116. (Previously Presented) The method of claim 110, wherein pro-inflammatory cytokine concentrations resulting from the method are lower as compared to the pro-inflammatory cytokine concentrations resulting from an equivalent therapeutically effective reduction in blood glucose concentration achieved by subcutaneous injection of insulin.

117. (Currently Amended) The method of claim 110, wherein the delivery agent 4-[(4-chloro, 2-hydroxybenzoyl)amino]butanoic acid is a compound having the formula:



or a pharmaceutically acceptable salt thereof, wherein

i. X is a halogen or hydrogen;

ii. R is substituted or unsubstituted C1-C12 alkylene, or a substituted or unsubstituted C1-C12 alkenylene.

118. (Currently Amended) The method of claim 117, wherein the delivery agent is ~~4-[(4-chloro, 2-hydroxybenzoyl)amino-butanoic acid or~~ a derivative or analog ~~thereof~~ of 4-[(4-chloro, 2-hydroxybenzoyl)amino]butanoic acid .

119. (Previously Presented) The method of claims 110, wherein the insulin is selected from the group consisting of recombinant human insulin, bovine insulin, porcine insulin and functional equivalents thereof.

120. (Currently Amended) A method of treating diabetes and reducing the incidence and or severity of hyperinsulinemia associated with chronic dosing of insulin, comprising orally administering on a chronic basis to a diabetic patient a dose of insulin and a delivery agent 4-[(4-chloro, 2-hydroxybenzoyl)amino]butanoic acid that facilitates the absorption of the dose of insulin from the gastrointestinal tract to provide therapeutically effective control and/or reduction in blood glucose concentrations, and a mean systemic plasma insulin concentration of the diabetic patient that is reduced relative to the mean systemic plasma insulin concentration provided by subcutaneous injection of insulin in an amount effective to achieve equivalent control and/or reduction in blood glucose concentration in a population of human diabetic patients.

121. (Previously Presented) A method of reducing the incidence and/or severity of one or more disease states associated with chronic administration of insulin, comprising treating diabetic patients via oral administration on a chronic basis with a therapeutically effective dose of a pharmaceutical composition which comprises insulin and a delivery agent 4-[(4-chloro, 2-hydroxybenzoyl)amino]butanoic acid that facilitates the absorption of insulin from the gastrointestinal tract, such that the pharmaceutical composition provides a therapeutically effective reduction in blood glucose and a peak serum insulin concentration of the diabetic patient that is reduced relative to the peak serum insulin concentration of an equivalent therapeutically effective reduction in blood glucose concentration achieved by subcutaneous injection of insulin.

122. (Currently Amended) The method of claim 121, wherein the disease state is cardiovascular disease, and wherein the method provides a reduced expression of genes associated with vascular disease as compared to the level of expression of genes associated with vascular disease resulting from an equivalent reduction in blood glucose concentration achieved in a population of patients via subcutaneous injection of insulin.

123. (Previously Presented) The method of claim 122, wherein the genes associated with vascular disease are selected from the group consisting of early response genes, genes associated

with cytokines, genes associated with adhesion molecules, genes associated with lipid peroxidation, genes associated with thrombosis and combinations thereof.

124. (Previously Presented) The method of claim 123, wherein the early response genes are selected from the group consisting of c-myc, jun B, Egr-1, Ets-1 and combinations thereof.

125. (Previously Presented) The method of claim 121, wherein the disease state is selected from the group consisting of a neuropathy, a nephropathy, a retinopathy, an arteriopathy, atherosclerosis and combinations thereof.

126. (Previously Presented) The method of claim 121, wherein the disease state is selected from the group consisting of coronary artery disease, hypertensive cardiomyopathy and congestive heart failure.

127. (Previously Presented) The method of claim 110, wherein said disease state is vascular diseases.

128. (Currently Amended) A method of treating diabetes and reducing the incidence and or severity of hyperinsulinemia associated with chronic dosing of insulin, comprising orally administering on a chronic basis to a diabetic patient a dose of insulin and a delivery agent 4-[(4-chloro, 2-hydroxybenzoyl)amino]butanoic acid that facilitates the absorption of the dose of insulin from the gastrointestinal tract to provide a therapeutically effective reduction in blood glucose and a peak serum insulin concentration of the diabetic patient that is reduced relative to the peak serum insulin concentration of an equivalent therapeutically effective reduction in blood glucose concentration achieved by subcutaneous injection of insulin.

129. (Currently Amended) A method of reducing the exposure of the vasculature of diabetic patients to hyperinsulinemic conditions, comprising orally administering an oral insulin treatment comprising a dose of insulin together with a delivery agent 4-[(4-chloro, 2-hydroxybenzoyl)amino]butanoic acid which facilitates the absorption of said insulin from the gastrointestinal tract on a chronic basis to diabetic patients to reduce blood glucose levels in said diabetic patients by a desired amount, such that the concentration of insulin circulating in the

blood of said diabetic patients as a result of insulin treatment is reduced relative to the peak serum insulin concentration of an equivalent therapeutically effective reduction in blood glucose concentration achieved by subcutaneous injection of insulin.

130. (Currently Amended) A method of attenuating processes resulting from the reaction to a mild injurious stimulus in multiple areas of the response to increases in mRNA during insulin treatment, comprising orally administering an oral insulin treatment comprising a dose of insulin together with a delivery agent 4-[(4-chloro, 2-hydroxybenzoyl)amino]butanoic acid which facilitates the absorption of said insulin from the gastrointestinal tract on a chronic basis to diabetic patients to reduce blood glucose levels in said diabetic patients by a desired amount, such that the concentration of insulin circulating in the blood of said diabetic patients as a result of insulin treatment is reduced relative to the peak serum insulin concentration of an equivalent therapeutically effective reduction in blood glucose concentration achieved by subcutaneous injection of insulin.

131. (Currently Amended) A method of treating diabetic patients, comprising orally administering an oral insulin treatment comprising a dose of insulin together with a delivery agent 4-[(4-chloro, 2-hydroxybenzoyl)amino]butanoic acid which facilitates the absorption of said insulin from the gastrointestinal tract on a chronic basis to diabetic patients to reduce blood glucose levels in said diabetic patients by a desired amount, such that the concentration of insulin circulating in the blood of said diabetic patients as a result of said oral insulin treatment is not substantially greater than normal physiological levels.